REMARKS

Claims 67-76 have been added. Therefore, claim 48-76 are pending in the present application. Claims 67-76 are supported by claims 48-66 and the specification.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance. Reconsideration of the application in view of the above amendments and the following remarks is requested.

I. The Rejection of Claims 48-50, 56-59, 65 and 66 under 35 U.S.C. 102 or 103

Claims 48-50, 56-59, 65 and 66 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Ladner et al. (U.S. Patent No. 5,223,409). This rejection is respectfully traversed.

Ladner et al. disclose a method of producing phage libraries of variants by controlled random mutagenesis ("variegation") and then selecting phages bearing those variants that do not bind to a target. The variants are selected by being placed in an antibody column and phages bearing those variants that do not bind to the column are collected and cultured.

However, Ladner et al. do not disclose or suggest the methods of the present invention, which comprise mapping one or more epitopes of the reference protein and forming a DNA molecule encoding the variant, which has an altered amino acid sequence of one or more epitopes of the reference protein, wherein the variant evokes a lower immunogenic response in an animal than the reference protein.

The variants selected by Ladner et al. would likely contain multiple mutations, including mutations that are not in any epitope. Ladner et al. do not provide any information on how the skilled artisan would identify which of these mutations would be to an epitope or which of the mutations would belong to the same epitope. Thus, Ladner et al. do not map one or more epitopes of a reference protein.

Hence, Ladner et al. do not disclose or suggest a method comprising mapping one or more epitopes of the reference protein followed by forming a DNA molecule encoding a variant, as claimed herein.

Moreover, it is well known to persons of ordinary skill in the art that a large number of variants (typically ranging from 5-90%) produced by random mutagenesis, are not functional, e.g., due to improper folding of the protein, truncation of the gene by inadvertently introducing a stop codon, or disruption of stability. Since these nonfunctional variants are much less likely to bind to an antibody column than functional variants, the selection method used by Ladner et al. actually

increases the percentage of variants that are not functional. Hence, it is very unlikely that the method proposed by Ladner et al. would lead to any meaningful information on which mutations in a protein result in lower antigenicity, let alone lower immunogenicity.

Moreover, the variants that would be selected by the method of Ladner et al. do not bind to the target, i.e., the method described by Ladner et al. seeks to identify variants that have reduced antigenicity. Ladner et al. do not disclose methods for selecting variants that have reduced immunogenicity, i.e. the tendency of a variant to induce specific antibody production in an animal, or reduced allergenicity, i.e. the tendency of a variant to induce specific IgE antibody production in an animal.

Applicants note that Ladner et al. are interested in selecting variants that have increased binding to the target, however, the Ladner et al. reference contains one brief section (from column 102, line 44 – column 103, line 30) on selecting variants that do not bind to the target. Ladner et al. do not contain any working examples of selecting variants that do not bind to the target. Applicants, therefore, submit that Ladner et al. is not an enabling reference.

For the foregoing reasons, Applicants submit that the claims overcome these rejections under 35 U.S.C. 102 and 103. Applicants respectfully request reconsideration and withdrawal of the rejections.

II. The Rejection of Claims 51-53 and 60-62 under 35 U.S.C. 103

Claims 51-53 and 60-62 are rejected under 35 U.S.C. 103(a) as being obvious over Ladner et al. in view of either Zachariae et al. (Allergy, Vol. 36, pp. 513-516 (1981)) or Arlian et al. (Int. Arch. Allergy Appl. Immunol., Vol. 91, pp. 278-284 (1990)). This rejection is respectfully traversed.

As provided in Section I, Ladner et al. do not teach or suggest the methods of the present invention. Applicants submit that Zachariae et al. and Arlian et al. fail to cure the deficiencies of Ladner et al.

Zachariae et al. disclose that exposure to detergent enzymes like Esperase® will cause IgE-mediated sensitization in persons.

Arlian et al. disclose that Alcalase and Savinase cause respiratory allergy. However, Arlian et al. is also silent with respect to teaching the method, as claimed herein.

However, neither Zachariae et al. nor Arlian et al. teach or suggest methods for producing a DNA molecule encoding a variant of a reference protein, comprising mapping one or more epitopes of a reference protein and forming a DNA molecule encoding a variant, which has an

altered amino acid sequence of one or more epitopes of the reference protein, wherein the variant evokes a lower immunogenic response in an animal than the reference protein.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 103(a). Applicants respectfully request reconsideration and withdrawal of the rejection.

III. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

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